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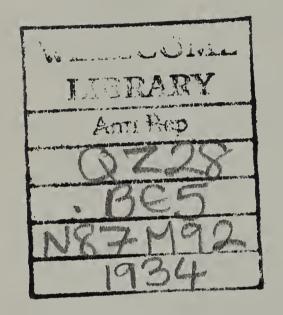## FOR THE TREATMENT OF CANCER,
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Statistical Report.

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SARCOMA OF BONE.

By STANFORD CADE, F.R.C.S.

Since the formation of the Registry of Bone Sarcoma in America in 1920 a vast amount of material was collected, sifted and preliminary conclusions drawn from the data which became available. For the clinical recognition of the various manifestations of the disease, a simple classification based on the work of the Sarcoma Registry is given here.

Bone sarcoma can be grouped in the following four categories:

1. Osteogenic sarcoma.
2. Ewing's tumour.
3. Giant-celled tumour.
4. Myelomatosis.

These four groups present different clinical pictures, pursue different clinical courses, and require different treatment.

The parosteal tumour is not a bone tumour. It is a fibro-sarcoma arising in the vicinity of or from the outer layers of the periosteum. The prognosis in this type of tumour is very much better than in bone sarcoma. A extra-periosteal chondro-sarcoma, a multilocular locally malignant tumour can be added to the main four groups to complete the classification.

Osteogenic Sarcoma.

This term includes the common varieties of sarcoma of bone classified in the pre-registry days as " periosteal " and " endosteal." It is now accepted that these two terms are of little practical value as no osteogenic sarcoma is entirely periosteal or endosteal, both structures being involved by the disease. This group is the commonest type of bone sarcoma. The tumour is a true osseous neoplasm derived from bone-cells or cells destined to become bone. Histologically they present a picture of spindle-celled sarcoma in a stroma of intercellular substance which is of great variety even in the same tumour: hyaline, fibrous, cartilagenous, osteoid and osseous tissues being all represented. Their behaviour as regards the skeletal part of their host—or the bone in which they originate is twofold: (1) they may destroy the parent bone—the osteolytic type; (2) they may cause bone formation (calcification, ossification)—the osteoblastic type. The appearances produced by the two give widely different radiological pictures. As a rule the osteoblastic type is more common in children and the reverse is the case in adults. The incidence of osteogenic sarcoma is relatively great; of all sarcomata they are the most frequently met with and occur in Great Britain in the proportion of 1 to 75,000 of population. They are more frequent in men than in women in the proportion of 4 to 3. The majority of cases occur in the early twenties; children are frequently affected, the disease being somewhat more common after the age of ten.

Site of the Disease.

The neighbourhood of the knee joint is the commonest site; two thirds of all cases affect the lower limb; 50 per cent. occur in the femur and 25 per cent. in the tibia. The lower end of the femur is affected four times as often as the upper end. The order of frequency in which the various bones are affected is as follows: femur, tibia, humerus, inominate bone, fibula, scapula, hands, feet, ulna, radius, ribs, jaws, vertebrae, skull.

Symptomatology.

The most common, the first and most persistent symptom of osteogenic sarcoma is PAIN. Although the first symptom, it is not an early symptom, its appearance precedes but little that of the lump. A history of slight trauma is obtained in many cases. A tumour develops, as a rule at the end of the long bones; in most cases it is fusiform, sometimes lobulated. The skin shows little abnormality with the exception of dilatation of veins.

Radiography.

Most osteogenic sarcomata show a combination of periosteal and endosteal involvement which contrasts with benign tumours which are either inside or outside the bone. The characteristic periosteal involvement appears in the form of striae, parallel to each other but at right angles to the long axis of the bone. The endosteal changes are either " osteolytic " or " osteoblastic " so that defects in the bone or additional bone may be present.

The fusiform tumours show up well in skiagrams; the shaft although permeated by tumour is not distorted or displaced, it is seen traversing the tumour. At the edges of the tumour a shelf of bone is lifted up giving a characteristic appearance. Invasion of soft tissues is visible in the skiagrams and lines of calcification are seen at the periphery of the tumour at some distance from the bone.

Diagnosis of Osteogenic Sarcoma.

Effect of Biopsy.

This is a controversial subject. Opinions vary in different anatomical sites and different schools. Ewing states that the objections to a biopsy are numerous and serious:—" The incision releases pressure and is usually followed by an acceleration of growth. In many vascular tumours there is uncontrollable or serious hæmorrhage. It is often difficult to obtain the tissue from a suitable portion of the growth and erroneous diagnosis results. Finally the structure of bone sarcoma is extremely varied and few pathologists have had sufficient experience to render a competent opinion from a small portion of bone."

It must therefore be emphasised that biopsy is never permissible in cases of osteogenic sarcoma. There is a natural tendency of bone sarcoma to form widely spread visceral and skeletal metastases but there is an impression, perhaps not amounting to scientific evidence, but so strong in the minds of a great many clinicians that it amounts to a " clinical " certainty, that to explore an osteogenic sarcoma with the knife (and even with the diathermy) is to hasten the end of the patient. Further, whereas there is no known case of spontaneous fungation of these tumours through the skin, it does occur after biopsy if the limb is not amputated. Diagnosis therefore must depend on clinical and radiological findings.

Ewing's tumour.

One of the results of the intensive study of bone sarcoma by the American Registry was the identification of a class of sarcoma occurring in bone as a special clinical and pathological entity. It was the recognition of this by Ewing that led to the name " Ewing's Tumour." Before the classification adopted to-day, the pathologist described a " round-celled sarcoma " of bone, it is now recognised that such cells do not occur in osteogenic sarcomata, and that these tumours are really Ewing's tumours. The histological appearances of this tumour are typical.

The variety of cells constituting the matrix of an osteogenic sarcoma is entirely absent. The tumour consists of round or polyhedral cells with a small nucleus and clear cytoplasm. A characteristic feature is the apparent absence of intercellular material. The origin of the tumour cells is presumably the endothelial lining of the bloodvessels. The gross appearance is a mass of soft white or grey tissue, like brain substance or jelly and may at first be mistaken for pus. It occupies the central part of the bone and spreads up and down the shaft and outside it. It forms about 10 per cent. of all malignant bone tumours; it is 3 times commoner in males than in females. The age incidence is 5 to 10 years, the same incidence as osteomyelitis. The characteristic site is the cancellous tissue. The bones are affected in the following order of frequency:—tibia, humerus, femur, fibula, clavicle; of the small bones the os calcis is the favourite site.

Symptomatology.

This is very characteristic but misleading in its likeness to chronic osteomyelitis. Pain is the first and most important symptom, as in osteogenic sarcoma, but differs in character and also in the fact that it is intermittent at first. Rises of temperature accompany the attacks of pain. Pain precedes the tumour appearance by several months.

Radiology.

The X-ray appearances are typical. They show involvement of the shaft of the bone; the central cavity is widened; the cancellous tissue is destroyed; new endosteal bone formation is absent but the priosteum is thickened and forms new bone, which is laid down on its outer aspect in longitudinal lamellæ.

Diagnosis.

It is important to bear in mind the resemblance of this disease to osteomyelitis. The differentiation is of the utmost importance, and many a tumour has been explored under the impression that it was inflammatory and the disease hastened thereby. From osteogenic sarcoma, Ewing's tumour is distinguished by the situation, the radiographic appearances, the intermittency of the pain, the age incidence and chiefly by the extreme radiosensitivity of the Ewing's tumour; this is so marked that before an exploration is contemplated X-radiation or external radium should be tried. If the lesion is a Ewing's tumour it will respond rapidly to treatment and literally melt away. Another characteristic is that metastases occur not only in the lungs but in other bones, especially in the skull.

Giant-celled Tumour.

By this term is meant a tumour of bone, characteristic in its microscopical appearance, situation, life history and incidence. The older names for it were giant-celled sarcoma, myeloid sarcoma, or myeloma. This multiplicity of names led to confusion and was also quite inaccurate. It is not a true sarcoma, being only locally malignant, it is not a myeloma (tumour originating in the bone marrow) and this term is now reserved for multiple primary tumours; therefore the term " myeloid sarcoma " was a misnomer both as to the aetiology and character of the tumour. The typical histological structure of the giant-celled tumours shows spindle-celled cells and characteristic giant-cells; these have multiple nuclei situated in the centre and not at the periphery of the cell or at one end so differing from the giant-cells of foreign bodies or tuberculosis. The giant-cells are embedded in a stroma of spindle-cells and blood vessels. The incidence of giant-celled

tumours is half that of sarcomata. Most cases occur in young adults, the favourite age being 16 to 25; this differs from osteogenic sarcoma and Ewing's tumours. Sex incidence is equal.

Site.

The lower limb accounts for 56 per cent. of all giant-celled tumours; about 60 per cent. of these occur in the lower end of the femur and the remainder in the tibia, mostly all in the upper end. The commonest site therefore is either above or below the knee. Of remaining cases half occur in the upper limb and half in trunk and jaws. About 10 per cent. occur in the jaws.

Symptomatology.

Pain is frequent but less intense than in other forms of bone tumours. The first symptom is *tumour*. On examination the tumour is found near the *ends* of long bones, it is spherical in shape, painless on palpation; the bone is distended with tumour, the remaining normal bone forming a thin shell at the periphery; egg-shell crackling is common and characteristic. The general health is unimpaired; the tumour is always single. In the jaws the endosteal or medullary type rapidly distends the bone; another type is parosteal and forms a tumour below the mucous membrane which is clinically known as epulis.

Radiography.

As the tumour destroys the bone, it gives rise to typical X-ray appearances. The bone is widened; the cortex is a thin shell; coarse trabeculae are seen across the space occupied by the tumour. The limit between healthy and diseased tissue is well defined. The appearances are unlike those of any other bone tumour, but as the tumour degenerates, the radiographic findings become similar and sometimes indistinguishable from those of localised osteitis fibrosa, or a cyst in the bone.

Diagnosis.

The correct diagnosis can as a rule be established on the radiological appearance, the site of the tumour, the expansion of the bone, the egg-shell crackling. The tumours should be considered benign or only locally malignant but a few authenticated cases of metastasis have been described. Pre-operative diagnosis is important, as conservative treatment gives good results both by surgery and radiation.

Myelomatosis.

This term should be reserved for the clinical entity characterised by the simultaneous development of multiple tumours, chiefly in the flat bones. The term *myeloma* should not be used in cases of giant-celled tumour. Myelomatosis is a rare disease, the rarest of the four main types of sarcoma of bone. It is a tumour of bone marrow, like Ewing's tumour, but presents a totally different syndrome. The disease is characterised by the multiplicity of tumours, all primary bone tumours. It is of high order of malignancy and kills the patient in two years at the most. The microscopic appearance is that of rounded polyhedral cells with an eccentric nucleus and no intercellular material. The cells resemble closely the plasma cell. The marrow cavity is expanded and filled with a mass of soft tumour reddish grey in colour. Myelomata do not metastasize in the lungs. The incidence of the disease is rare and the age incidence is higher than in other forms of bone sarcoma; 80 per cent. of myelomata are found in patients over 40 years of

age; the usual age is between 40 and 60. Men are affected twice as frequently as women.

Site.

The distribution of the lesions is chiefly in the bony walls of the thorax, sternum, ribs, vertebrae. Next in frequency are the skull, the pelvis and the clavicle. Long bones are the least frquently affected, and here the disease starts in the centre of the shaft. Pathological fracture is a common complication, as bone destruction is marked and there is no bone formation.

Symptomatology.

Pain is the outstanding feature of the disease. At first vague and transient it recurs at shorter intervals and with greater intensity till it is continuous and very severe. It is frequently mistaken for lumbago as in most cases it starts in the back or in lumbar and sacral regions. General health is impaired, there is progressive emaciation and weakness; in the ribs, clavicle and some long bones the tumours are palpable. Pathological fractures are common, paraplegia is not infrequent. Metastases in the viscera are very rarely found, if present they occur in the spleen and liver and not in the lungs as in other forms of bone sarcoma.

Radiography.

The appearances in skiagrams are not unlike those of secondary deposits in bones. The affected bones show round or oblong translucent areas with or without pathological fractures. Periosteal reaction with bone formation is very exceptional, the characteristic feature is bone destruction.

Diagnosis.

The multiplicity of the tumours and their distribution are the chief diagnostic features. The differential diagnosis is between multiple secondary deposits of carcinoma and the multiple changes occurring in bones associated with parathyroid tumours. Anaemia is a feature of the disease. A diagnostic aid may be found in the presence of a peculiar albumose in the urine, known as Bence-Jones Albumosuria. This gives the following reaction: a cloud appears on heating the urine to 55°C, it disappears on further heating to 85°C and reappears on cooling. Sixty-five per cent. of cases of multiple myeloma give a positive Bence-Jones test. It is not absolutely specific as it is also found in leukemia and in cases with secondary deposits of carcinoma in bones.

The following table shows the main features of the four common types of primary malignant disease of the bones. It was compiled with the object of contrasting the clinical manifestations and life-history of the four groups and shows the very marked differences between them:

MAIN CHARACTERISTICS OF THE TYPES OF BONE SARCOMA.

Type	Incidence	Age (years)	Sex	Types of bones affected	Order of frequency	Site of origin in bone	Metastases	Site of Metastases	Radiographic appearance
Osteogenic Sarcoma	Common 50% of all bone tumours	10—20	$\frac{M}{F} = \frac{4}{3}$	Long bones (any bone)	1. Femur 2. Tibia 3. Humerus 4. Pelvis 5. Fibula 6. Scapula	Ends (Metaphysis)	Very frequent	Lungs Other bones	Bone Formation and Bone Destruction
Ewing's Tumour	10% of bone tumours	5—15	$\frac{M}{F} = \frac{3}{1}$	Short bones also Long bones	1. Tibia 2. Humerus 3. Femur 4. Fibula 5. Clavicle 6. Os Calcis	Centre Shaft (Diaphysis)	Frequent	Skull bones Lungs	Bone Destruction Slight Bone Formation Vertical striation
Giant celled Tumour	25% of all bone tumours	16—25	Equal	Long bones and Jaws	1. Femur 2. Tibia 3. Jaws	Lower end Upper end Centre Epiphysis	Never (with very few exceptions)		Bone Destruction
Myeloma	Rarest of all	40—60	$\frac{M}{F} = \frac{2}{1}$	Flat bones	1. Ribs 2. Vertebræ 3. Sternum 4. Skull 5. Pelvis 6. Clavicle 7. Long bones	Centre	Terminal manifestation	Spleen Liver	Bone Destruction

TREATMENT.

It is acknowledged to-day as it was twenty years ago that the treatment of malignant tumours of bone is unsatisfactory. It is often quoted and is well known that of the 200 cases of osteogenic sarcoma accepted by Codman's Registry only 12 five-year cures were obtained, and of these twelve, nine were atypical in structure and their malignant character was doubted by some of the pathologists of the registry. It is therefore no light task to attack the treatment of this formidable type of tumour by methods untried and in which the technique is still in its infancy. The results of surgical treatment of bone sarcoma require no comment and no excuse is needed in trying out other forms of treatment; of these there is only one which offers something to the patient, namely radiation; it should not be used to displace surgery, any more than surgery should be used to the exclusion of radiation. The view that all operable cases of bone sarcoma should be submitted to operation and radiation reserved for the inoperable group is obsolete and the results of surgery do not warrant it. The very bad results of surgery and the nearly equally disappointing results of radiation were however fruitful in the establishment in 1920 of the American Bone Sarcoma Registry. In the 15 years which have elapsed since then the majority of pathologists, a good number of surgeons and a few—very few—general practitioners have become familiar with the work of the Registry. The outstanding advances made in those 15 years are chiefly the recognition of different types of tumour of bone, a better knowledge of the natural history of each type, the interpretation of radiographic evidence and the variation in their response to treatment by the various groups. Nomenclature as well as the actual classification has undergone changes and a great deal of the original classification has had to be discarded, at least by the clinician.

To assess the value of radiation in the treatment of bone sarcoma it is necessary to consider the behaviour of these types of tumours when submitted to radiation, the nature of the response, how this can be ascertained clinically and to analyse the methods of irradiation employed. For this purpose I have scrutinised very carefully 37 cases of bone sarcoma; of these 25 cases were treated at Westminster Hospital, 19 under my care and 6 under my colleague, Mr. Rock Carling, who very kindly gave me access to the notes and all other data. The remaining 12 cases were treated at Mount Vernon Hospital, 4 under my care and 8 under other members of the staff, and I am indebted to Sir Cuthbert Wallace for the full records of these. An analysis of these cases shows as follows :—

	Total	Alive	Dead
Osteogenic Sarcoma	26	6	20
Ewing's Tumour	5	2	3
Giant-celled tumour	3	3	0
Myelomatosis	1	0	1
Chondro-sarcoma	2	1	1

Of the total of 37 cases, 12 are alive and so far free from disease for the following periods of time :—

1.	Osteogenic sarcoma of femur (No. 1263)	5 years
2.	Giant-celled tumour of Tibia (No. 394)	5 ,,
3.	Osteogenic sarcoma of Tibia (No. 719)	4 ,,
4.	Ewing's tumour of Malar (No. 794)	3 ,,

5. Giant-celled tumour of Femur (——)   3 years
6. Ewing's tumour of Femur (No. 934)   3   ,,
7. Giant-celled tumour of Femur (L/A)   2   ,,
8. Osteogenic sarcoma of Tibia (G/M.V.)   2   ,,
9. Osteogenic sarcoma of Scapula (A/R.C.)   2   ,,
10. Osteogenic sarcoma of Humerus (No. 1357)   1   ,,
11. Chondro-sarcoma of Femur (No. 1544)   1   ,,
12. Osteogenic sarcoma of Tibia (No. 1460)   1   ,,

Before discussing the methods of treatment the following point in connection with the clinical aspect of bone sarcoma must be mentioned: effect of the tumour on the bone.

Effect of the tumour on the bone.

Bone formation in sarcoma of bone is incidental and not essential; a true bone tumour may completely destroy the osseous tissue of its host. On the other hand bone formation is not uncommon and both calcification and ossification are sometimes taken as characteristic of certain bone lesions. The appearances of various tumours of bones as seen in radiograms are familiar to all surgeons, but it may be interesting to emphasise the following points:

The subdivision of bone sarcoma into the *osteolytic* and *oeteoblastic types* is of interest. As regards degree of malignancy it has no significance, but as regards the degree of sensitivity to radiation it is of great importance; osteolytic tumours are the more radiosensitive. R. Watson-Jones and R. E. Roberts in a lucid and very complete study on Calcification, Decalcification and Ossification have shown:

(1) That there is normally a balance between the calcium content and the vascularity of mesenchymatous tissues.

(2) That in the case of bones:

> Normal circulation   =   normal calcification.
> Increased blood supply   =   decalcification.
> Decreased blood supply   =   increased calcification.
> Blood supply cut off   =   unchanged calcification.

(3) Fibroblasts + excess of calcium + adequate blood supply = bone.

These conclusions based on pathological and biochemical observations are fully supported by clinical evidence; they bear great importance on the problem of radiation of bone sarcoma.

In tumours which are osteolytic in character, the blood supply is always increased, the rate of growth is rapid, the degree of malignancy is therefore indirectly increased.

To produce inhibition of growth, retrogression of the tumour and finally restoration to normal three factors are necessary: (1) Decrease of blood supply, (2) Increase of calcium, (3) Inhibition of mitosis. Further it is an absolute *sine que non* that these changes should be produced aseptically, atraumatically and at a rate which suits the particular tumour. Radiation is capable of altering the rate of growth, it materially affects the blood supply and it promotes the formation of fibroblasts—but it must be very skilfully administered. Calcium of course can be given to the patient at will. The normal process of repair is the calcification

and ossification of both the tumour and the bone from which it arises. In tumours of the osteoblastic variety the conditions are different, the radiosensitivity is of a lower degree, the treatment is capable of increasing the rate of growth, and technique and dosage are so important that full familiarity both with the disease and radiation is essential if disaster is to be avoided. Besides the bone forming and the bone destroying types, there is the sclerosing variety of neoplasm—chiefly seen in metastatic tumours of bone from primary growth of non-osseous origin.

The actual mechanism by which radiation produces the changes from tumour tissue into normal structure such as bone is unknown; the process of repair as seen in a series of radiograms in cases of the periosteal variety of osteogenic sarcoma is as follows:—the interstices between the bony spicules situated at right angles to the long axis of the affected bone become filled with new bone so that instead of a series of bony spicules there appears gradually a thick layer of bone produced from the periosteum; this new bone shrinks, the process being similar to that seen in the formation of callus in a fracture and the subsequent disappearance of the external callus. In the osteoblastic type the new bone increases in density and instead of being distributed in patches throughout the neoplasm becomes uniform and finally shrinks. In the osteolytic type new and apparently normal bone is formed and replaces the tumour. If one were to conjecture as to the actual process which transforms an osteogenic sarcoma into a mass which at first resembles an osteoma and later normal bone, both from the X-ray appearances and from the histological sections the process of arrest of the disease would appear to be as follows:—the matrix of the tumour or stroma is composed of bony, cartilagenous and fibrous tissue, this can be considered as the normal response of bone to the presence of malignant cells under certain conditions; the actual neoplasm consists of typical sarcoma cells, spindle-shaped in the osteogenic type, round-celled in Ewing's tumour. The effect of radiation under ideal conditions is to arrest mitosis in these cells; once these cells are no longer actively dividing, the stroma cells invade the spaces occupied by the altered malignant cells, the process being identical to that seen in the tongue, uterus or breast irradiated for carcinoma. Radiation if correctly carried out does not cause death of malignant cells in the sense of necrosis and sequestra formation as is the case in osteomyelitis, but absorption of some cells and pressure atrophy of others by the normal bone cells, fibrous tissue and cartilage.

The desired result of calcification can be obtained in most cases by careful treatment. All trauma, especially surgical incision should be avoided. Large doses of calcium should be given daily throughout the period of treatment and maintained in diminishing doses for about three months after the cessation of radiation. Radiation should be intermittent, uniform throughout the affected part and prolonged over several weeks (up to two months). A combination of radium and X-ray treatment or X-rays appears to be more effective than either agent alone and it is possible that radiosensitivity can be increased by a variation in the wavelength used. A combination also permits an increase of total dosage up to 50 per cent. Repeated skiagrams control the effect of the treatment. Absolute rest of the affected part, especially avoiding weight-bearing in the lower limb, generally diminishes the blood supply and enhances calcification.

Treatment by Radiation.

Radiation treatment of bone tumours can be given by X- or y-rays or a combination of both. It must be remembered that radiation of bone tumours

is still in the experimental stage and that no hard and fast rules are applicable. It is therefore essential that the radiation treatment of bone tumours should be in the hands of the very experienced radiotherapeutist and that the possession of the apparatus—even 5 grammes of radium or a million volt machine—by incompetent or inexperienced persons is not likely to lead to any good results. Inefficient radiation will never arrest the disease, in some cases it may undoubtedly stimulate it. Excessive irradiation especially in bone tumours will cause the gravest accidents and the treatment becomes worse than the disease. All the methods of irradiation available in radiotherapy are applicable to bone tumours but not all of them are necessarily suitable. As far as X-radiation is concerned, by itself it is of great value, in combination with radium it is of greater value still. The cases referred to earlier were treated by various methods and it is on the results obtained that the opinion here expressed is based.

Interstitial Radium Treatment.

It has no place in the treatment of bone tumours. All the objections to a biopsy are applicable to needling. All the objections to this method in the treatment of sarcoma elsewhere hold good. All the objections based on the study of damage and repair point to the ineptitude of attempting such treatment. I have no hesitation in saying this as I have practised it and abandoned it with maturer experience.

Of the eleven cases so treated two only are alive: one a giant-celled tumour of the tibia in which amputation of the leg had to be done following the necrosis and sepsis resulting from the interstitial irradiation; the other an osteogenetic sarcoma of the malar bone and jaws repeatedly operated on where a preliminary external radiation was followed by needling.

The other nine cases are all dead and are as follows:—

Osteogenic Sarcoma of Jaw—locally very much worse after needling—died with severe sepsis the growth progressing *pari passu* with extensive necrosis.
Myelomatosis—local temporary improvement.
Osteogenic Sarcoma involving vertebræ—local temporary improvement.
Osteogenic Sarcoma of Fibula—necrosis—amputation—metastases.
Osteogenic Sarcoma of Scapula—died of sepsis.
Sarcoma of Ileum—extensive local disease persists.
Osteogenic Sarcoma of Femur—died from sepsis and local disease—no metastasis.
Sarcoma of Ileum—vast local disease.
Osteogenic Sarcoma of Femur—exhausted by pain, toxæmia and persistence of local disease.

It is hardly possible that the technique only was at fault—four different surgeons cannot always be guilty of the same errors of technique. It is the method which is at fault and should be condemned and abandoned in the treatment of bone sarcoma in England, as it has been abandoned in all other countries.

Surface Radiation by plaques.

The rationale of this method is sound but the results are poor owing to the difficulty of delivering the correct tissue-dose accurately and in the right period

of time. A plaque to be of use should contain about 200 mg., be applied at a distance of at least 4 cm., preferably more, its construction should be a matter of at least as much precision as the construction of a denture of artificial teeth. In my series it was used six times—with the exception of one case—myeloma referred to already as having had interstitial radiation as well, all the patients are dead. Two patients lived in comfort for three years and two years respectively, the latter became pregnant, and was delivered of a normal child before recurrence took place.

Mass Radiation.

Distance radiation with large quantities of radium, teletherapy or bomb, is the method of choice. It is safe both to the patient and personnel, it permits of protraction and fractioning of the dose, it is easily combined with X-radiation which is of very great advantage. By this method—with the 4 gm. bomb and the smaller units nineteen patients were treated and of these seven are alive and free from disease, one for five years; one for four years; two for three years; one for two years; and three for one year.

Process of repair.

The changes occurring after radiation by X- or y-rays are as follows:— there is a progressive shrinkage of the growth; gradual ossification of the tumour; deposition of calcium in the centre of the lesion; re-establishment of the normal structure in the parent bone; healing of pathological fractures. The end result is a somewhat thickened, sclerosed bone, in some cases normal in shape but increased in size, in others there is an apparent transformation of the malignant tumour into a bony mass, not unlike an osteoma or a chondroma.

Prognosis.

It is known to all that unfortunately these changes are not often permanent and local recurrence takes place in the majority of cases; when they occur they do not do so in the centre of the original growth, but at its periphery, and a second and sometimes a third generation of tumours can easily be seen in skiagrams. The development of metastasis in a patient whose lesion has healed with radiological treatment is as likely as after amputation. It is therefore necessary in the treatment of bone tumour to control the local and general condition of the patient by frequent radiological and clinical examination, and further treatment is dictated by the clinical manifestations.

In Osteogenic Sarcoma.

Radiation by slow external method should be given. As long as the tumour retrogresses there is no indication for further treatment. If no response is obtained amputation must follow radiation. If recurrence takes place a second radiation should precede amputation. In all cases radiation of the chest by X-rays is to be carried out. It is important to point out that radiation of the chest should be a mild treatment; the pulmonary metastases from bone sarcoma are very sensitive and do not require high intensities.

In Ewing's tumours.

Radiation is the method of choice—the extreme radiosensitivity of the tumours is a characteristic of the disease, the histological appearance suggests an endothelial or plasma-celled tumour and makes it particularly suitable for

radiation. Prophylactic radiation of the chest is of lesser importance than in the osteogenic tumour.

In the giant-celled tumour.

My own personal experience with radium has been unfavourable, but I am apparently unlucky as others report, chiefly from the United States, that radiation is now nearly always preferred to surgery. There is no doubt that good results have been obtained but I have very little personal experience of it.

In Myelomatosis.

Surgery is inapplicable—there is only radiation or the pseudo-medicinal treatment; I prefer the former as it relieves pain, leads to ossification of the tumours and renders life a little more bearable till further tumours terminate the patient's life.

In Chondro-Sarcoma.

Parosteal cartilaginous tumours, multilocular, partially encapsuled—surgery is the method of treatment, but conservative surgery, consisting of enucleation of the tumour followed by external radiation.

In conclusion I think it can legitimately be held that radiation has added a little hope to the patient with malignant bone tumour. It has given the clinician a new method of treatment which deserves further exploration, and with Codman I would like to conclude with the hope that future sufferers from bone sarcoma may be fortunate enough to fall into the hands of radiologically minded surgeons.

THE DEVELOPMENT FROM 200 TO 900 kV.
ROENTGEN THERAPY.

A REPORT ON AMERICAN HIGH VOLTAGE X-RAY INSTALLATIONS VISITED DURING FEBRUARY AND MARCH, 1935.

By L. H. GRAY, Prophit Scholar of The Royal College of Surgeons of England, at The Mount Vernon Hospital.

The voltage commonly employed for deep therapy in this country at the present time is 200 kV. A number of X-ray tubes have been operating at 400 kV. for some time in Great Britain and elsewhere, but clinical installations operating at higher voltages have hitherto been confined to the United States of America.

The problem of generating a current of a few milliamperes at voltages of the order of one million volts is one upon which engineers have been engaged for a number of years, and there are available to-day a number of very satisfactory and reliable types of installation. The construction of an X-ray tube which will operate smoothly at such voltages, however, has proved a difficult task.

By 1932 Coolidge, Dempster, and Tanis of the General Electric Co., had installed in the Memorial Hospital, New York, an X-ray tube operated by a large induction coil,

which was used for two years at between 600 and 700 kV. peak voltage, and Lauritsen had set up in the California Institute of Technology a tube which operated on unrectified alternating current from a transformer, at 550 kV. peak voltage.

Both tubes were used for clinical treatment. As was to be expected, technical defects interfered with clinical treatment on numerous occasions. Looking over the daily records at the Memorial Hospital, and bearing in mind the magnitude of the undertaking, it was surprising to find the number of days and even weeks in which there was no interference with treatment. Apart altogether from any clinical information that was obtained, which certainly was not negligible, these first tubes were of immense value in indicating how the technical difficulties could be overcome. The Memorial Hospital tube, after passing through one intermediate stage, has resulted in the tubes now in daily operation at 800 kV. (pulsating voltage) at the Mercy Hospital, Chicago, and the Swedish Hospital, Seattle. Lauritsen's tube has been marketed by the Kelleket Co. as a tube operating on direct current, constant potential. A tube of this type is now working very satisfactorily and smoothly at 500 kV. with entirely negligible interruption of clinical work at the Harper Hospital, Detroit. A second tube has been pushed to 600 kV. by the physicist at the General Hospital, Lincoln, Nebraska, but at this voltage the output is not very steady.

This type of tube consists of a single porcelain transformer bushing, having a target at one end at ground potential, and a filament supported inside a steel tube running down the length of the bushing from the narrow end (top) at which the high voltage is applied. It was designed by Lauritsen for voltages only of the order of 500 kV., and experience seems to show that it is unwise to attempt to push the voltage to higher values.

If it is intended that the tube should be operated at higher voltages it is better to follow the procedure of Lauritsen who, finding this type of tube satisfactory up to 500 kV., built a second tube in the Kellog Radiation Laboratory, consisting essentially of two of these tubes placed end to end, one extending about eight feet above, and the other an equal distance below the treatment room, the target and filament being supported in steel cylinders running axially from the top and bottom of the whole system to within nine inches of the middle of the tube. The centre part of the tube, running from floor to ceiling of the treatment room, is a steel cylinder about 50 cm diameter, at ground potential. The radiation emerges through four ports, two horizontal at a convenient height above the floor, and two inclined downwards at 14 degrees to the horizontal. The tube is operated by unrectified alternating current at 925 kV. peak voltage. Since equal and opposite voltages are applied to each end of the tube, no connection outside the tube is at more than half this voltage. Nevertheless it is impossible to eliminate corona discharge altogether, but since everything inside the treatment room is at ground potential, and the room can be hermetically sealed and air-conditioned, there is no trace of ozone or nitrogen oxides to cause sickness. The room is artificially illuminated. The operation of the tube is controlled in a separate room.

The insulating part of the tube consists of a series of glass cylinders cemented to steel plates with shellac. The glass walls are protected from electron bombardment by wide steel cylinders, and the tube is continuously evacuated by diffusion pumps. Originally, of course, mercury diffusion pumps were used, and it was necessary to place a " trap " containing liquid air between the pump and the tube to freeze out mercury vapour which would otherwise reach the tube. The development of diffusion pumps using heavy organic oils, by Birch of Metropolitan Vickers, has been no small contribution to the technical development of these tubes, in that higher pumping speeds are now

possible, and the expense of liquid air is eliminated because the trap is no longer necessary. Oil diffusion pumps are now used on all the high voltage installations.

The continuous evacuation of the tube has two main consequences. On the one hand it is an extra quantity to be "controlled" by the technician operating the tube. Lauritsen's tube, being "home-made," is by no means proof against puncture of the insulation. The vacuum therefore has to be watched, and occasionally punctures have to be mended by a new coat of shellac. Experience has shown up the principal weak points, so that leaks are usually discovered in the course of a minute or two, and once the hole has been painted over, the pumps, being rapid, soon restore the vacuum to a working value. It fortunately happens that this type of tube operates best when the vacuum is relatively poor, so that a puncture rarely causes a delay of more than five to ten minutes. By proper design, however, punctures can be practically entirely eliminated, as is shown by the fact that the tubes at Detroit, Chicago, and Seattle, which have each been in operation more than eighteen months, have never yet been punctured. In such cases the vacuum control amounts only to a periodical (three-monthly) inspection of pumps, and a check at the beginning of each day. During the treatment, the vacuum gauge requires only an occasional glance.

In Detroit, for safety, the pumps are run continuously, but it appears that this is not really necessary if arrangements can be made for a gauge to be read and the pumps to be switched on (an "unskilled" operation) about one and a half hours before the commencement of treatment. This plan is adopted at all places other than Detroit.

Continuous evacuation, on the other hand, has the advantage that, in the event of the burning out of filament or target (the two principal fatalities of X-ray tubes) the parts may be replaced at negligible cost in the course of one day, and treatment continued the following day. The cost and even possibly the delay is in marked contrast with that incurred if the whole X-ray tube has to be replaced, as is the case with the sealed-off tube used at lower voltages.

It is a little remarkable that, in the tube operated by rectified potential, viz., Detroit, Lincoln, Los Angeles, Chicago, and Seattle, the valves are not also continuously evacuated. Metropolitan Vickers have continuously evacuated valves in satisfactory operation in Sheffield and Manchester, and in this respect their system for generating high voltage seems preferrable to that in use in the American installations.

During the past two years treatment has only had to be discontinued at Pasadena on account of technical faults, on about four or five days. Thirty to forty patients are treated a day, in groups of three or four at a time. In general the intensity of the radiation, measured in air and without backscatter at a distance equal to the normal focal skin distance (70 cm) is 15 r per minute, and a treatment usually lasts 20 minutes. The tube is thus in clinical operation for an average of about 1,400 hours a year, during which time about 11,000 treatments are given.

The tube at Seattle (General Electric Co.) is built to the same design as that at Chicago, but embodies a few small technical improvements. As measured by the length of spark between large spheres, which is the standard of the American Institute of Electrical Engineers, the peak voltage under full load (10 mA) is 850 kV. under present working conditions. It is probable that the sphere gap scale is somewhat in error, so that this is really only 800 kV.

The generating plant consists of four Villard circuits cascaded, so that the resultant

potential varies between o and 800 kV. during one half cycle, and remains zero during the other.

The X-ray tube differs from the type of tube at Pasadena chiefly in that the filament and target are at the extreme ends of the tube, and the electron stream, which therefore travels a total path of about ten feet, is accelerated in four stages by a set of coaxial cylinders inside the evacuated glass tube. The target is at ground potential and the filament is at -800 kV. at the peak of the voltage cycle. Since the voltage is applied in four stages there is not more than 200 kV. between adjacent electrodes ; spurious discharges within the tube are minimised, and puncture of the glass walls is practically impossible. On the other hand, the long electron path makes the focussing of the beam on the target by means of auxiliary magnetic fields a rather delicate matter, and the tube requires a very good vacuum.

The installation was completed in October, 1933. A special building was erected, comprising a room 27 ft. high by 27 ft. by 35 ft. for the tube and generating plant, a treatment room 6 ft. 6 ins. high by 6 ft. by 9 ft., a laboratory and other accessory rooms.

Treatment was commenced in January, 1934, at 590 kV. By March, sufficient experience had been gained in the handling of the tube, and certain small alterations had been made, which enabled the voltage to be raised to 710 kV. and again in August to 750 kV. In February of this year the voltage was further raised to 850 kV. I saw the tube operating very smoothly at this voltage, and it was likely that the tube would stand higher voltages if the generating plant were adequate.

Since the current through the tube is large (10 mA.) and the filament is set back in its support so that very little current is drawn at low voltages, there is a good output of medium and high voltage radiation, making it possible to use 2·7 mm. lead filtration, and thereby obtain a good quality radiation. Only rough quality measurements have so far been made, but these indicate an average wavelength of about 0·04 A°.U. which may be compared with 0·10 A°.U. obtained by filtering a 200 kV. constant potential tube with 1 mm. copper and 0·013 A°.U., the average wavelength of the radium γ-rays filtered through 0·5 mm platinum.

Under present conditions the output, measured in air without backscatter, is 60 r per min. at 70 cm. and treatment is carried out at this intensity. The tube is horizontal, and the beam of radiation is vertical and fixed in direction. Thus only one patient can be treated at a time, but on account of the high intensity, the actual treatment time (5 min.) is only one quarter of that at Pasadena for the same dose. The treatment room is artificially illuminated and air-conditioned.

From the time the tube was installed it has averaged 850 hours a year of clinical service, but this is considerably exceeded now that the tube is in full running order.

In both this type of installation and that at Pasadena, the cost of operation is represented by a power consumption of about 15 kW. (excluding illumination of building) together with renewal of parts. The renewal of filaments, target, and oil for the diffusion pumps will amount to only a few pounds a year at most. At Seattle, as pointed out above, the cost of valves is more serious. No valves are used at Pasadena.

In the University Hospital, San Francisco, D. H. Sloan of Berkeley University has built an installation on entirely different principles. The secondary coil of a high frequency transformer in which the high voltage is generated, is contained inside a large

steel tank, which is also the X-ray tube. The secondary coil is hung from the top of the tank, and has a target on the bottom (high potential) end, to which electrons are accelerated from a filament in the side of the tank. The potential of the target varies between + and — 900 kV. with respect to the tank (ground potential). The emission of the filament is so controlled that current only passes to the target when the voltage of the latter is in the neighbourhood of + 900 kV. In practical use the chief points of difference between this and the other installations are as follows :—

The tube is operated by two very powerful valves similar to those used in wireless transmission. The valves are of special design, continuously evacuated, and can be relatively easily taken apart for replacement of filament, which is necessary after about 500 hours of use. The power consumption of the whole installation for an output equal to that of the Pasadena or Seattle installations is about 100 kW.

Since 900 kV. difference of potential exists across a single gap inside the tank, it is imperative that the vacuum be kept very good. If the vacuum is not good enough, spark over occurs. There is no insulation to be punctured, but the resonance circuit becomes detuned, and the voltage drops to zero. About 30 secs. to a minute must be allowed for removal of gas before the voltage is applied again. I happened to visit the installation the next day after the tank had been opened up. The vacuum had not been restored to a high value, and spark over occurred on numerous occasions in the course of the morning. The tube was then operating at about 600 kV. By the afternoon, the vacuum had improved sufficiently to enable the voltage to be increased to 700 kV., and it was anticipated that in the course of the next or the following day, the tube would be working again at 900 kV. I was informed that it had been in operation for a month at full voltage without interruption, just prior to my arrival. The overall average hours of treatment is 650 hours a year (commencing August, 1934), or 800 hours a year, counting only the last six months—figures approaching sufficiently closely those of Pasadena and Seattle to show that the tube has already emerged from the stage of a technical experiment.

An important feature of this type of installation is the small space which it requires. At San Francisco the treatment room is 18 ft. long, 12 ft. wide and 7 ft. 6 ins. high. The tank (4 ft. diam. and 4 ft. high) which is both high voltage generator and X-ray tube in one, is suspended from the ceiling, and is fitted with horizontal and inclined ports, and one vertical port. This room and one of similar size for the controls, pumps, etc., is all the space required, and is in marked contrast with the very large buildings which have been specially erected for the tubes at Pasadena, Chicago and Seattle.

There being a considerable want of uniformity in the measurement of output and quality for the various types of tube, no fine distinctions can be made, but it would appear that in both respects the San Francisco tube, working at full voltage, is at least the equal of the tubes at Pasadena and Seattle, *i.e.*, that it is approximately the equivalent of a 900 kV. tube.

At the present moment it is somewhat less reliable in operation, but it must be remembered that it is the youngest of the tubes. The history of all the tubes at present in operation has been very similar, comprising an initial period of about three months during which clinical treatment was carried out with many interruptions and generally at less than full voltage. During this period a number of technical defects made themselves apparent, even when the tube was a replica of a former tube installed elsewhere, for all tubes have a certain individuality. Then follows a somewhat longer period during which clinical treatment is only occasionally interrupted, but in which the tube

still requires a little coaxing, and the physicist in charge is still fully occupied. Finally the idiosyncrasies of the tube are understood, troubles can be foreseen by slight departures from the normal behaviour, and remedied at a time when the tube is not required for treatment, so that during treatment the running of the tube is entirely a mattter of routine, and can be left to a technician. All the installations which I saw, leave at least a few working hours of every day free from clinical work for any repairs or adjustments. Broadly speaking, the installations at Detroit, Chicago, Pasadena* and Seattle, are in this latter stage, and those at Lincoln and San Francisco are in the second stage. A second installation of the San Francisco type is in the course of erection for Dr. Carter Wood in the Columbia University Medical School, New York, and is intended for operation at a peak voltage of about 900 kV. For a final comparison it would probably be necessary to wait a year. It would seem safe, however, to conclude already that any of the three types of installation are inherently capable of good regular clinical service up to peak voltages of the order of a million volts.

It is interesting that in the course of four years the gap from 200—900 kV. should have been bridged successfully in three quite different ways.

Although high (peak) voltages are applied to the X-ray tubes, the quality of the resultant radiation which is used clinically is rarely much better than the equivalent of a wavelength of 0·035 A°.U. or three times the average wavelength of the radium γ-rays. An improvement in quality could be effected if treatment were carried out at lower intensity, simply by the addition of more lead filtration, or by a simultaneous increase in the current through the tube and of the filtration. There are also other possibilities which might be explored, so that with the present peak voltages it should be possible to attain a hardness at least equivalent to the softer component of the radium γ-rays (0·02 A°.U.).

Very few measurements of the absorption of high voltage X-radiation in tissue-like substances have been made, but the scanty data available indicate a small increase in "depth-dose" as compared with that for 200 kV. radiation. The improvement is more marked in the case of small fields.

It also seems certain that radiation from a 900 kV. tube does markedly less damage to the skin than an equal dose of radiation from a 200 kV. tube, when both doses are measured in air and *without backscatter.* How far this is due to a difference in the amount of radiation scattered back through the skin by the body in the two cases, and how far it is due to a different biological effect of different wavelengths, has not yet been determined. Nor has it been shown how far the ability to deliver a greater dose, resulting from this increase in "skin tolerance" has improved clinical results. Some improvement is claimed by all radiologists who have used both types of radiation, but the claims of those whose experience is longest are conservative, indicating the need for further experiment.

* The Pasadena installation is operated by engineering or physics students of the California Institute of Technology, many of whom have no special experience, but reference can always be made to a more experienced person. The installation should therefore perhaps be classed as intermediate between stage two and stage three. With a little trouble and the expenditure of a little money, it could undoubtedly be transformed into an instrument which could be handled in a routine manner by a technician.

INSTITUTIONS VISITED.

THE MEMORIAL HOSPITAL, NEW YORK.
Two-section tube operated by an induction coil at 700 kV. A four-section tube somewhat similar to that in operation at Seattle is to be installed.

THE HARPER HOSPITAL, DETROIT.
Single-section tube operating at 500 kV. constant potential.

THE MERCY HOSPITAL, CHICAGO.
Four-section tube operated by pulsating current at 800 kV. peak voltage.

THE GENERAL HOSPITAL, LINCOLN, NEBRASKA.
Single-section tube operating at 600 kV. constant potential.

THE SOILAND CLINIC, LOS ANGELES.
Single-section tube operated formerly by unrectified alternating current at 440 kV. peak voltage. A 600 kV. constant potential generator is being installed to be used in conjunction with the same tube.

THE KELLOG RADIATION LABORATORY, PASADENA, CALIFORNIA.
Tube operated by unrectified alternating current at 900 kV. peak voltage.

THE UNIVERSITY HOSPITAL, SAN FRANCISCO.
The Sloan high frequency generator and tube operating at about 900 kV. peak voltage.

THE SWEDISH HOSPITAL, SEATTLE.
Four-section tube operated by pulsating current at 850 kV. peak voltage.

DEPARTMENT OF EXPERIMENTAL PATHOLOGY, 1934.

The following investigations have been carried out during the year :—

(1) ON THE ALTERATION IN THE SENSITIVITY OF CELLS TOWARDS RADIATION PRODUCED BY COLD AND BY ANAEROBIOSIS.

Crabtree and Cramer have shown that tumour cells are rendered more sensitive by cold, and less sensitive by anaerobiosis. This was confirmed using bean roots for both gamma radiation and X-radiation. It is evident, therefore, that these results have wide biological application and are of much importance.

Since gamma radiations in exposures of about a hundred minutes, and X-radiation in exposures of about forty seconds both show these alterations in sensitivity, it follows that differences in ability to recover are unlikely to account for these alterations.

Crabtree and Cramer have radiated tumour cells under a number of other controlled conditions and their general conclusion is that it is the state of the respiratory mechanism at the time of radiation which largely determines the sensitivity of the cell. If this prove to be the case, then it should be possible to determine which part of the mechanism of cellular respiration is especially acted upon, and therefrom guide attempts to make tumour cells more sensitive to radiation. Reference Brit. J. Radiology 1934, VIII., No. 25, 32.

(2) SOME EFFECTS OF CANCER PRODUCING AGENTS ON CHROMOSOMES.

The mutation hypothesis for Cancer, postulates that the Cancer cell differs from the normal cell in its content of genes. If such be the case, then the most likely cause is undoubtedly some disturbance during mitosis in the regular distribution of genes to the daughter cells, associated with abnormal behaviour of chromosomes.

Bean roots were exposed to a number of cancer producing agents and subsequently the chromosomes examined for irregular distribution. In all cases these were abundantly found; however, such changes occur, as is well known, under many other experimental conditions in no wise related to Cancer producing agents. If Cancer producing agents produce cancer by action on genes or chromosomes, then tar for instance, when painted on the skin, may differ from other agents which affect chromosomes but do not cause cancer, in being able to penetrate the horny layers of the skin and so act upon the living basal layer of cells. It may be that some such property as this determines whether or no substances are capable of producing cancer, and not upon some peculiar direct action of them on living cells. Reference Brit. J. Exp. Path. 1934, XV. 71.

(3) On the Correlation between Malignancy and the Rate of Growth of Tar Warts in Mice.

This investigation deals with the natural history of tar warts in mice. A great number of their characters were closely observed at frequent intervals during their life; the data thus obtained was analysed and many conclusions drawn. The more important of these had to do with growth rate, and with the result of autografting. It was observed that warts formed a continuous series, from those growing most quickly to those of the slowest growth rate; that malignant warts were for the most part fast-growing and benign slow-growing, with a decided overlap in this respect; that the warts showed remarkable regularity in growth rate over long periods of time, indicating that growth was a stable character; that occasionally sudden increase in growth rate seemed as if a benign wart was suddenly changed to a fast-growing malignant wart, this was, however, an uncommon occurrence; and furthermore evidence was found of the possibility that the occurrence was due to a fast-growing wart having origin so close to a slow-growing benign wart as to be indistinguishable from it on inspection.

The study of autografts, as with growth rate, showed that warts form a continuous series; at one end they give rise to epitheliomas on autografting, at the other end the benign warts do not grow on autografting; between the two, the series is completed by warts which give rise to epithelial cysts, some of which are simple cysts, some cysts with thickened walls of epithelial cells, and some cysts difficult to classify into either malignant or benign.

Autografts also show that some warts are only malignant locally, since both epitheliomas and simple epithelial cysts result from their inoculation.

The outcome of the investigation indicates that the Cancer problem, at any rate as regards tar cancers in mice, embraces two subsidiary problems it is necessary to account for (1) the occurrence of a single series of tumours varying from malignant at one end to benign at the other, and (2) the occurrence of what determines innocence and what malignancy within this series.

As regards the first problem, the present findings stress the necessity of accounting for benign tumours side by side with cancers; and as regards the second problem, they suggest that the growth rate of the tumour cells may alone determine innocence or malignancy. Reference American J. Cancer 1934, XXII. 801.

J. C. Mottram.

DEPARTMENT OF DEEP THERAPY.

THE REPORT OF THE WILLIAM MORRIS FELLOW.

BRIEF ACCOUNT OF THE WORK CARRIED OUT IN THE DEEP THERAPY DEPARTMENT OF THE HOSPITAL DURING THE YEAR 1934.

During the year 263 complete courses of treatment were administered to 167 patients.

The time taken for a complete course varied from one to four weeks, in different cases.

The number of fractional doses given was 3410.

The different types of case came under the following main groups :—

(1)	Brain tumours	3
(2)	Cranial bones	4
(3)	Upper air passages	35
(4)	Breast	27
(5)	Oesophagus	7
(6)	Thorax	8
(7)	Gynaecological	36
(8)	Prostate	8
(9)	Urinary tract	11
(10)	Abdomen	11
(11)	Bone sarcoma	3
(12)	Various	14
		167

Of the above 167 cases 94 were treated by a combination of Radium and X-rays, and the remainder, 73, were treated by X-rays only.

As regards results there has been some degree of improvement in nearly all types of cases, the most marked improvement being in those breast cases, which were treated with X-rays only, the majority of these cases have been advanced and many inoperable, nearly all having extensive involvement of the axillary and supraclavicular glands, several also having varying degrees of skin involvement, with ulceration.   In about 75 per cent. of these cases there has been complete disappearance of the primary growth and glands as revealed by clinical examination, some of these cases extending over a period of two years from the commencement of treatment.

Summary of Research Work carried out during the year 1934.

1.   Further modification of technique and dosage have been carried out. The initial intensive split dose has been increased in the majority of cases and the period of saturation dose has been lengthened.

2.   An attempt has been made in a number of cases to lower the vitality of malignant tissue by the introduction into the body, per os or by injection, of substances known to have a toxic effect on protoplasm. Such a compound has been chosen in order that in addition to its biological effect, its physical action may be to increase the secondary radiation in the tissues being irradiated. One such substance that has been used in a number of cases is quinine-hydrobromide, as likely to meet the above requirements. The results obtained indicate the desirability of further investigation.

3. The treatment of cases of malignant disease by x-radiation administered through openings made in the skin or deeper structures, as indicated in my report of last year, has been continued. Several cases of carcinoma of the rectum and of deep seated lesions in the neck have been treated in this way, and the results obtained are encouraging.

4. Investigations into the properties of "Short Waves" are being carried out with special reference to :—

(*a*) Any specific action they may have on cell life and on the malignant cell in particular excluding any effects directly due to heat formation.

(*b*) The possibility of combining "Short Wave" therapy and x-radiation, either simultaneously or in sequence.

<div align="right">G. CRANSTON FAIRCHILD.</div>

DEPARTMENT OF PATHOLOGY, 1934.

During 1934 the total number of specimens examined was 905, as compared with a total of 680 in 1933. This increase was shared by all branches of the work, but the largest increase was seen in the number of ward blood-counts, which rose from 125 to 240.

Post-mortem examinations numbered 32. In addition, 890 routine urine examinations were made, but since September 1st, 1934, these have been done on the wards.

Specimens from the Theatre, Wards and Staff were made up as follows :—

Histological Examinations	271
Blood Counts—Staff	187
„ „ Wards	240
Urines, Special Tests	28
Exudates, pus, etc.	44
Blood—Serological tests	57
Biochemical Estimations	40
Throat Swabs, Sputa, etc.	38
Total	905

<div align="right">THOS. H. PULLAR.</div>

TABLE I., 1934.

A TABULAR STATEMENT SHOWING THE CONDITION ON DECEMBER 31st, 1934, OF ALL CASES TREATED AND DISCHARGED FOR THE FIRST TIME IN 1934.

Site.		Disease.	Methods of Radiation and Other Treatment.		Total.	Male.	Female.	Alive.	Dead.
			Primary Growth.	Lymph Areas.					
LIP		Sq. Carc.	I.	I.	1	1		1	
		,, ,,	I.	S.	2	2		2	
		,, ,,	I.	SX.	2	1	1	2	
		,, ,,	S.		1	1		1	
					6	**5**	**1**	**6**	
TONGUE	Anterior	,, ,,	I.	I.	1	1		1	
	Middle	,, ,,	I.	I.	3	3		3	
	,,	,, ,,	I.	S.	1	1			1
	,,	,, ,,	I.	S. SX.	1	1			1
	,,	,, ,,	I.	SX.	2	2		2	
	,,	,, ,,	SX. I.	S.	1		1		1
	Posterior	,, ,,	I.		2	2		1	1
	,,	,, ,,	I.	I.	2	2		1	1
	,,	,, ,,	I.	S.	2	2		2	
	,,	,, ,,	SX.		1	1			1
					16	**15**	**1**	**10**	**6**
	Recurrent	,, ,,			3	3		1	2
	Leukoplakia		I.		2	1	1	2	
FLOOR OF MOUTH		Sq. Carc.	I.	S.	1	1			1
		,, ,,	I.	B. S.	1	1		1	
		,, ,,	SX. S.	S.	1	1			1
BUCCAL MUCOUS MEMBRANE			,, ,,	I.	SX.	1	1		1	
		,, ,,	I. S.		1		1	1	
PALATE		,, ,,	I.		2	2		2	
		,, ,,	I.	S.	1	1			1
		,, ,,	SX. I.	S. I.	1	1		1	
		,, ,,	SX. I.	I.	1	1			1
		,, ,,	SX. S.		1	1			1
		,, ,,	S.		1		1		1
					7	**6**	**1**	**3**	**4**
	Sarcoma	SX. I. S.		1		1		1	
	Papilloma	I.		1		1	1		
FAUCES		Sq. Carc.	I.		1	1			1

Figures in heavy type are the summation of the numbers in the immediately preceding category.

Symbols used to Denote Methods of Treatment.

B	Block Dissection.	IAbd	Interstitial *via* Abdomen.
C	Cavitary.	IO	Interstitial through wound.
E	Excision of Growth.	LA	Local Amputation.
F	Fenestration.	RA	Radical Amputation.
H	Heyman Technique.	S	Surface with Radium.
I	Interstitial.	SX	Deep Therapy.

TABLE I., 1934 (continued).

Site.		Disease.	Methods of Radiation and Other Treatment. Primary Growth.	Lymph Areas.	Total.	Male.	Female	Alive.	Dead.
TONSIL		Sq. Carc....	I.		2	2		2	
		,, ,,	I.	E. I.	1	1		1	
		,, ,,	I.	S.	1	1		1	
		,, ,, .	E. I.	S.	1	1		1	
		,, ,, ..	SX. I.	SX.	1		1	1	
		,, ,, ..	Nil	Nil	1	1		1	
					7	**6**	**1**	**7**	
	Recurrent	Sarcoma		S.	1	1			1
PYRIFORM FOSSA		Sq. Carc....	SX.	I.	1	1			1
		,, ,,		I.	1	1			1
POST CRICOID		,, ,,	SX.		2	1	1		2
		,, ,,	Nil	Nil	1	1			1
PAROTID		Carc.	I.	I.	1	1		1	
		,,	SX. I. SX.		1		1	1	
	Recurrent	,,	SX.		1	1		1	
SUB MAXILLARY		Endothelioma	E.		1		1	1	
CERVICAL GLANDS	Secondary	Sq. Carc.		I.	2	2		2	
		,, ,,		S.	1	1		1	
	Primary	,, ,,		SX. I.	1	1			1
		,, ,,		SX.	1	1			1
ŒSOPHAGUS		,, ,,	SX.		3	3		1	2
		,, ,,	Nil	Nil	1	1			1
MOUTH	Recurrent	,, ,,			3	3		1	2
STOMACH			SX.		2	2			2
RECTUM		Col. Carc.	C.		1	1		1	
		,, ,,	I.		2	2			2
		,, ,,	SX. I. SX.		1	1			1
		,, ,,	I. C.		1	1		1	
		,, ,,	C. I.		1		1		1
		,, ,,	SX.		1	1			1
		,, ,,	Colostomy		3	3			3
		,, ,,	E.		2	1	1		2
					12	**10**	**2**	**2**	**10**
SIGMOID	Recurrent	,, ,,	SX.		1		1	1	
		Actinomycosis	S.		1	1		1	
NASAL FOSSA		Sq. Carc....	I.		1	1		1	
		,, ,,	F. I. S.		1		1	1	
		Sarcoma	I.		1		1	1	

Figures in heavy type are the summation of the numbers in the immediately preceding category.

Symbols used to Denote Methods of Treatment.

B	Block Dissection.	IAbd	Interstitial via Abdomen.
C	Cavitary.	IO	Interstitial through wound.
E	Excision of Growth.	LA	Local Amputation.
F	Fenestration.	RA	Radical Amputation.
H	Heyman Technique.	S	Surface with Radium.
I	Interstitial.	SX	Deep Therapy.

TABLE I., 1934 (continued).

Site.		Disease.	Primary Growth.	Lymph Areas.	Total.	Male.	Female.	Alive.	Dead.
Sup Maxilla ...	....	Sq. Carc....	SX. S.	....	1	1		1	
	Recurrent	,, ,, ...	....	....	2		2	1	1
Larynx	Intrinsic	,, ,, ..	SX.	....	1	1		1	
		,, ,, ...	SX. F.I.	....	1	1		1	
	Extrinsic........	,, ,, ...	SX.	....	1	1		1	
		,, ,, ..	SX.	....	1	1			1
		,, ,, ..	*Nil*	*Nil*	2	2		1	1
Lung	....	....	SX.	....	4	4		1	3
			Nil	*Nil*	1		1		1
Thyroid...	....	Carc.	S.	....	1		1	1	
		,, ...	S.X.	....	2	1	1	2	
		,, ...	SX. S.	....	1	1		1	
Breast	....	Sp. Carc. ...	I.	I.	6		6	6	
		,, ,, ..	SX. I.	I.	1		1	1	
		,, ,, ...	S.	....	1		1	1	
		,, ,, ...	S.	S.	3		3	3	
		,, ,, ..	SX.	SX.	6		6	5	1
		,, ,, ...	RA. S.............	S.	1		1	1	
		,, ,, ..	RA.	S.	1		1	1	
		,, ,, ...	LA. I.	I.	2		2	2	
		,, ,, ..	LA. I. S.	I. S.	2		2	2	
		,, ,, ...	LA. S.	I. S.	2		2	2	
		,, ,, ..	E. I..............	I.	1		1	1	
		,, ,, ..	S. E. I.	I.	1		1	1	
			RA.	RA.	1		1	1	
					28		**28**	**27**	**1**
	Palliative	Sph. Carc. ..	RA. S.....	S.	2		2	2	
		,, ,, ..	LA. I.	I. S.	1		1		1
		,, ,, ..	S.	S.	3		3	3	
		,, ,, ..	S. I..............	S.	1		1	1	
		,, ,, ...	SX.	....	2		2		2
		,, ,, ...	SX.	SX.	1		1		1
					10		**10**	**6**	**4**
		Col. Carc. ..	LA.	....	1		1	1	
	Previous R.A....	Sph. Carc. ..	S.	S.	14		14	14	
	,, ,,	,, ,, ..	....	S.	3		3	3	
	,, ,,	,, ,, ...	SX.	SX.	1		1	1	
	,, ,,	,, ,, ..	....	SX.	1		1	1	
	Prev. Radiation	,, ,, ..	S......	S.	1		1	1	
	Recurrent	,. ,, ..	....	....	17		17	15	2
	Various	....	....	....	2		2	2	

Figures in heavy type are the summation of the numbers in the immediately preceding category.

Symbols used to Denote Methods of Treatment.

B	Block Dissection.	IAbd	Interstitial *via* Abdomen.
C	Cavitary.	IO	Interstitial through wound.
E	Excision of Growth.	LA	Local Amputation.
F	Fenestration.	RA	Radical Amputation.
H	Heyman Technique.	S	Surface with Radium.
I	Interstitial.	SX	Deep Therapy.

TABLE I., 1934 (*continued*).

Site.		Disease.	Methods of Radiation and Other Treatment. Primary Growth.	Lymph Areas.	Total.	Male.	Female.	Alive.	Dead.
VULVA............	....	Sq. Carc...	I.	....	3		3	3	
		,, ,, ..	I.	S.	1		1	1	
		,, ,, ...	S. E. I.	S.	1		1	1	
		,. ,, ...	... .	S.	1		1	1	
					6		**6**	**6**	
		Leukoplakia	E. SX.	....	1		1	1	
		,,	C. I.	....	1			1	1
	Sec. Glands......	Sq. Carc....	....	S.	1		1		1
CERVIX	....	,, ,,	H.	....	15		15	9	6
		,, ,,	H.	SX.	23		23	22	1
		,, ,,	C....	....	8		8	5	3
			Nil	Nil	1		1		1
					47		**47**	**36**	**11**
	Recurrent	,, ,,	....	....	3		3	2	1
		Papillomatosis	Hysterectomy	....	1		1	1	
CORPUS	....	Sph. Carc. ...	C....	....	3		3	3	
		,, ,, ...	C. SX.	....	1		1	1	
			C. Hysterectomy	....	1		1	1	
			SX.	....	3		3	2	1
			Nil	Nil	1		1		1
					9		**6**	**7**	**2**
OVARY............	....	Carc.	SX.	....	2		2	1	1
	Metastases	,, ...	S. X.	....	3		3	1	2
		Adenoma	E..............	....	1		1	1	
UTERUS	....	Hæmorrhage	C.	....	37		37	36	1
PROSTATE	....	Carc.	SX.	....	7	7		5	2
		,, ...	Nil	Nil	1	1		1	
	Various	....	SX.	....	2	2		1	1
PENIS	....	Sq. Carc...	I.	....	1	1		1	
		,, ...	I.	S.	1	1		1	
TESTIS	Recurrent	Teratoma......	I. SX.	....	1	1			1
			SX.	....	1	1			1
BLADDER	....	Carc.	I.	....	1	1		1	
		,, ...	I. SX.	SX.	1		1	1	
		,, ...	SX.	....	6	4	2	3	3
					8	**5**	**3**	**5**	**3**

Figures in heavy type are the summation of the numbers in the immediately preceding category.

Symbols used to Denote Methods of Treatment.

B	Block Dissection.	IAbd	Interstitial *via* Abdomen.
C	Cavitary.	IO	Interstitial through wound.
E	Excision of Growth.	LA	Local Amputation.
F	Fenestration.	RA	Radical Amputation.
H	Heyman Technique.	S	Surface with Radium.
I	Interstitial.	SX	Deep Therapy.

TABLE I., 1934 (*continued*).

Site.		Disease.	Methods of Radiation and Other Treatment. Primary Growth.	Lymph Areas.	Total	Male	Female	Alive	Dead
BLADDER (*continued*)	Recurrent	Carc.			5	3	2	3	2
		Papilloma	SX. I.		1	1		1	
KIDNEY	Recurrent	Carc....	SX.		1	1			1
SKIN		Rodent Ulcer	I.		8	5	3	8	
		,, ,,	E.		1		1	1	
	Recurrent	,, ,,			10	8	2	10	
		Epithelioma			2	2		2	
	Recurrent	,,			2	1	1	1	1
		Fibro-angeioma			1	1		1	
STERNUM	Type ?	Sarcoma	SX.		1		1	1	
TIBIA	Type ?	,,	S.		1	1		1	
HUMERUS	Spindle	,,	SX.		1	1		1	
MAXILLA		Myeloma	I.		1		1	1	
VARIOUS	Recurrent				7	2	5	6	1
NECK		Lymph-adenoma	SX.		1	1		1	
	Recurrent	Endothelioma			2	1	1	1	1
BLOOD	Myeloid	Leukaemia	SX.		1	1			1
CEREBRAL TUMOUR	Radiation only at Mt. Vernon				14	9	5	6	8
SPINAL TUMOUR	,, ,,				1	1		1	
MISCELLANEOUS					23	1	22	22	1
					404	146	258	305	99

Figures in heavy type are the summation of the numbers in the immediately preceding category.

Symbols used to Denote Methods of Treatment.

B	Block Dissection.	IAbd	Interstitial *via* Abdomen.
C	Cavitary.	IO	Interstitial through wound.
E	Excision of Growth.	LA	Local Amputation.
F	Fenestration.	RA	Radical Amputation.
H	Heyman Technique.	S	Surface with Radium.
I	Interstitial.	SX	Deep Therapy.

TABLE II.
TONGUE.
All Cases (untreated when first admitted).

Year.	Interval since Treatment.	Total.	Alive.	Dead.	Not Traced.
1930	4 years	16	1	15	
1931	3 years	17	2	15	
1932	2 years	10	4	6	
1933	1 year	9	2	7	
1934		16	10	6	

TABLE X.
RECTUM.
All Cases (untreated when first admitted.)

Year.	Interval since Treatment.	Total.	Alive.	Dead.	Not Traced.
1930	4 years	17	0	17	
1931	3 years	8	0	8	
1932	2 years	9	1	8	
1933	1 year	4	0	3	1
1934		12	2	10	

TABLE XX.
CARCINOMA OF BREAST.
All Cases (untreated when first admitted).

Year.	Interval since Treatment.	Total.	Alive.	Dead.	Not Traced.
1930	4 years	46	18	27	1
1931	3 years	55	23	32	
1932	2 years	51	28	23	
1933	1 year	47	25	22	
1934		39	34	5	

TABLE XX. A.
CARCINOMA OF BREAST.
PALLIATIVE TREATMENT AND NO TREATMENT CASES EXCLUDED.

Year.	Interval since Treatment.	Total.	Alive.	Dead	Not Traced.
1930	4 years	45	18	26	1
1931	3 years	47	21	26	
1932	2 years	42	27	15	
1933	1 year	40	24	16	
1934		29	28	1	

TABLE XX. B.
CARCINOMA OF BREAST.
INTERSTITIAL RADIATION OF BREAST AND LYMPHATIC AREAS.

Year.	Interval since Treatment.	Total.	Alive.	Dead.	Not Traced.
1930	4 years	23	8	14	1
1931	3 years	14	5	9	
1932	2 years	10	4	6	
1933	1 year	11	6	5	
1934		6	6	0	

TABLE XX. C.
CARCINOMA OF BREAST.
INTERSTITIAL AND SURFACE RADIATION OF BREAST AND LYMPHATIC AREAS.

Year.	Interval since Treatment.	Total.	Alive.	Dead.	Not Traced.
1930	4 years	10	4	6	
1931	3 years	20	8	12	
1932	2 years	20	15	5	
1933	1 year	10	7	3	
1934		0	0	0	

TABLE XXV.
CARCINOMA OF CERVIX.
All Cases (untreated when first admitted).

Year.	Interval since Treatment.	Total.	Alive.	Dead.	Not Traced.
1930	4 years	41	10	31	
1931	3 years	53	20	32	1 stage 2
1932	2 years	55	24	31	
1933	1 year	39	20	19	
1934		47	33	14	

TABLE XXV. B.
CARCINOMA OF CERVIX.
ALL CASES TREATED BY RADIATION.

Year.	Interval since Treatment.	INTERNATIONAL DEGREE.								Total.		Not Radiated.		Not Traced.
		1		2		3		4						
		Alive.	Dead.	Alive.	Dead.	Alive.	Dead.	Alive.	Dead.	Alive.	Dead.	Alive.	Dead.	
1930	4 years	4	3	4	6	2	11	0	10	10	30		1	
1931	3 years	3	1	6	7	10	14	1	10	20	32			1 stage 2
1932	2 years	7	2	6	1	8	9	3	18	24	30		1	
1933	1 year	2	0	2	3	13	8	3	8	20	19			
1934		5	1	8	2	12	2	8	8	33	13		1	